Anion-induced Water Flux as Drug Release Mechanism Through Cationic Eudragit RS 30D Film Coatings

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Karl G. Wagner[1] and Ronny Gruetzmann[1]

[1]University of Tuebingen, Institute of Pharmacy, Department of Pharmaceutical Technology, Auf der Morgenstelle 8, 72076 Tübingen, Germany

ABSTRACT

The objective of this study was to investigate the anion-controlled drug release mechanism through the cationic coating polymer Eudragit RS 30 D as a function of the anion attraction toward the polymer's quarternary ammonium group (QAG), anion valence, and film composition. The mechanism was investigated by dissolution testing, determination of chloride ion exchange using ion chromatography, plasticizer leaching by means of differential scanning calorimetry, and water uptake by Karl Fischer titration. All experiments were performed on coated theophylline micro tablets or isolated films of various compositions using 0.01 M sodium nitrate, sodium sulfate, disodium succinate, sodium acetate, and succinic acid as dissolution media. The mechanism of drug release involved an immediate penetration of dissolution medium into the polymer followed by an instant exchange of chloride against the medium's anion species at completely different rates compared with the drug release. Dependent on the attraction of the anion toward the QAGs, a water flux was induced by back and forth exchanging anions. Strong attraction (nitrate, sulfate) resulted in a low water flux while weak attraction resulted in a high flux (acetate, succinic acid). The water flux increased at increasing number of QAGs. Plasticizer acted as a diluent in respect of the number of QAGs, thus higher plasticizer concentrations led to lower drug release.

KEYWORDS: Eudragit, ion exchange, water uptake, plasticizer leaching

INTRODUCTION

With polymer-coating for sustained release oral dosage forms, drug release through the polymer membrane is diffusion controlled.[1] The diffusion is thereby dependent on the membrane permeability, which is seen as directly connected to the water uptake or swelling, respectively, of the polymer membrane.[1] This hydrogel hypothesis is widely applicable for swellable polymers like cellulose derivates (ethyl cellulose, cellulose acetate),[2-4] however, in the case of the cationic polymethacrylate Eudragit RS, a more complex drug release mechanism may exist. Depending on the ionic background of the dissolution medium, various drug release profiles could be triggered[5-7] through the ionic interaction of the cationic quaternary ammonium group (QAG) of the polymethacrylate and anions of the buffer solution. The polymer can act as a strong basic anion exchanger, and drug release was discovered to be inversely proportional to the selectivity coefficient of the anion species toward the QAG.[5] Knop[8] hypothesized a major influence of the anion's hydration shell, which was subsequently proven in our own work.[9] We additionally linked it to another hypothesis of smaller hydrated anion radii leading to stronger Coulomb forces between anions and QAGs, ie, a higher selectivity coefficient would result in decreased membrane permeability. Divalent anions have the ability to crosslink polymer chains and thus further obstruct membrane permeability. Via the limiting anion conductivity (λ_0^-) and the ion mobility (μ_0) the hydrated radius of anions can be calculated. Thus, the effect of any anion species on the permeability of Eudragit RS membranes could be predicted. Still, the following question remains: how is the ion exchange on the polymer's QAG related to the membrane permeability? In general, 2 mechanisms are possible: (1) the anion's hydration shell causes the water uptake and swelling of the polymer; the larger the hydration shell the higher the water uptake and the higher the membrane permeability,[8] or (2) the larger the hydrated radius of the anion the weaker the attraction towards the QAG and the shorter the time an individual anion is bound on a QAG until replaced by another of the same species. This latter mechanism would induce an ion "oscillation" inversely proportional to the attraction towards the QAG. Since the anions are traveling in water, a water flux toward and into the polymer would be the result, similar to an active carrier system in biological membranes.

The purpose of the presented work was, therefore,

1. to examine the relationship between hydrated anion radius, chloride ion exchange, and drug release, anions with a strong interaction toward the QAG like nitrate or sulfate, which should obstruct the drug release according to the hypothesis of Wagner and McGinity,[9] and
2. to determine the mechanism that relates drug release and ion exchange.

Corresponding Author: Karl G. Wagner, Tel: +49 7071 297 4558; Fax: +49 7071 29 5531; E-mail: karl.wagner@uni-tuebingen.de

Experimental Methods

Materials

The following chemicals were obtained from commercial suppliers and used as received:

1. Excipients for micro tablets

   Theophylline anhydrous powder 200 (Knoll, Ludwigsahfen, Germany), Avicel PH 101 (MCC) (FMC Co/Lehmann and Voss and Co, Hamburg, Germany), Aerosil200 (Degussa AG, Frankfurt/ Main, Germany), Kollidon 90 F (BASF AG, Ludwigshafen, Germany), magnesium stearate (Bärlocher GmbH, Unterschleißheim, Germany)

2. Excipients for film coating and isolated films

   Eudragit RS 30D (Röhm GmbH and Co KG, Darmstadt, Germany), triethyl citrate (= TEC, Röhm GmbH and Co KG, Darmstadt, Germany), Cutina GMS (glycerol monosterate) (Henkel, Düsseldorf, Germany), Talcum IT Extra (Norwegian Talc GmbH, Bad Soden-Salmünster, Germany), Tween 80 V (Polysorbate 80) (Uniquema, Wirral, UK)

3. Chemicals for analytical assays

   Succinic acid, disodium succinate anhydrous, sodium nitrate, sodium sulfate decahydrate, sodium acetate anhydrous, sodium carbonate anhydrous, sodium hydrogen carbonate, acetone (Merck KGaA, Darmstadt, Germany), Karl Fischer reagents (Hydranal 34801, 34803, 34757, 34800, formamide; Riedel-de Haën, Seelze, Germany), methanol (Fisher Scientific, Loughborough, UK)

Preparation of theophylline micro tablets

Batches of 167.2 g theophylline anhydrous powder and 232.8 g Avicel PH 101 were granulated with an aqueous solution of 6% Kollidon 90 F (200 g) as binder using a fluidized bed granulator (Uniglatt, Glatt GmbH, Binzen, Germany), which was equipped with a 0.8-mm nozzle. The atomizing air rate was 1.0 bar. The inlet air temperature was maintained constant at 70°C and the granulation liquid flow rate was set to 15 g/min controlled by a peristaltic pump (Model 505S, Watson Marlow, Falmouth, England). The granules were dried in the same apparatus for an additional 15 minutes at the same temperature. The granules were passed through a 500-µm sieve and further blended with 1% (wt/wt) magnesium sterate and 0.3% (wt/wt) Aerosil 200 for 10 minutes in a tumbling mixer (Turbula H2C, W. A. Bachofen, Basel, Switzerland). The micro tablets were compressed on an instrumented rotary tablet press (Korsch PH 230/17, Korsch AG, Berlin, Germany) using a force feeder. Two of the 17 punch stations were equipped with punch holders containing 19 concave punches of 2 mm in diameter and compression pressure was set to 168 MPa at 50 rpm machine speed. The band height of the tablet was 0.8 mm, hence micro tablets of 6.8 mg in weight resulted. Data acquisition was performed using the Compression Research System (Korsch AG, Berlin, Germany). Batches of 300-g micro tablets were then coated with various Eudragit RS 30D coatings (Table 1) at a polymer level of 8.9% (wt/wt) based on the dry polymer, at 2 plasticizer levels of 10% (wt/wt) or 20% (wt/wt) TEC using 2 different glidants: 5% (wt/wt) GMS or 50% (wt/wt) talc. Glidant and plasticizer were calculated on the basis of the dry polymer. The coating was performed in a fluidized bed coater (Model HKC 5, Hüttlin, Steinen, Germany), equipped with a 0.8-mm nozzle at an inlet air temperature of 40°C, an outlet air temperature of 31°C, and a spray rate of 5 g/min. The atomizing air rate was 1.0 bar. Following the completion of the coating process, the micro tablets were dried in the fluidized bed apparatus for additional 15 minutes. The coated micro tablets were cured for 24 hours at 40°C and then sealed in brown glass containers and stored at room temperature.

Determination of the QAG density

The density of QAGs ($n_{QAG,V}$) is the ratio of the moles of QAGs divided by the volume of the respective coating composition in cm^3. The weight-specific QAG number $n_{QAG,w}$ in pure polymer was calculated on the basis of the chloride weight fraction in the polymer (Equation 1) according to its

Table 1. Film Composition

		Micro Tablet Coatings				Isolated Films		
Name of Excipient	**Coat Function**	**A**	**B**	**C**	**D**	**I**	**II**	**III**
Eudragit RS 30D	Polymer (mg/cm^2)	4.75	4.75	4.75	4.75	20	20	12
TEC	Plasticizer (%)	10	10	20	20	20	20	20
GMS	Glidant (%)	—	5	5	—	—	5	—
Talc	Glidant (%)	50	—	—	50	50	—	—
Tween 80	Surfactant (%)	—	—	—	—	8	8	8

TEC, triethyl citrate; GMS, glycerol monosterate. Dashes (—) indicate that the excipient is not contained in the film composition.

compostion: ethylacrylate (EA) 10: methylmethacrylate (MMA) 20: trimethylammonioethyl methacrylate chloride (TMAEMACl) 1, where *n* is the number in moles and *M* the molecular weight of the respective monomer.

$$n_{QAG,w} = \frac{n_{Cl}}{n_{EA} \cdot M_{EA} + n_{MMA} \cdot M_{MMA} + n_{TMAEMACl} \cdot M_{TMAEMACl}} \quad (1)$$

The QAG number in the entire coating compositions volume was then derived from $n_{QAG,w}$ (311.4 µmol/g), mass and true density of all coating constituents according to Equation 2.

$$n_{QAG,V} = \frac{n_{QAG,w}}{\rho_{RS} + m_{Gl} \cdot \rho_{Gl} + m_{TEC} \cdot \rho_{TEC}} \quad (2)$$

Where *m* (g) denotes the mass and ρ (g/cm^3) the true density determined using a helium comparison pycnometer (Beckman, Fullerton, CA; $n = 3$, data not shown). The index RS represents the pure polymer Eudragit RS 100, Gl. the glidant (talc or GMS) and TEC the plasticizer.

Preparation of isolated films

Isolated films of various compositions (Table 1) were produced using a self-made automatic film application machine.[10] The films were prepared on the surface of exactly horizontal aligned polytetrafluoroethylene (PTFE) coated glass plates at a constant temperature of 30°C. Addition of Tween 80 V to the coating dispersion was necessary to support the dispersion's spreading onto the PTFE surface. The film dispersion was kept in an aluminum film applicator with a gap clearance of 0.8 × 150 mm. The film applicator moved with a constant drawing-down speed of 2.5 mm/s on the upper surface of the PTFE-coated glass plates. The film dispersion spread on the glass plate and the film-forming process started. To complete the film-formation process, isolated films were cured for 24 hours at 45°C. Films with a coating level of 20 mg/cm^2 displayed a thickness of 180 ± 5 µm; films of 12 mg/cm^2 were 110 to 130 µm.

Dissolution of Theophylline

Theophylline release from the coated micro tablets was determined during 8 hours using the Ph. Eur. 5/2005[11] paddle dissolution apparatus at a temperature of 37°C and 100 rpm (Sotax AT7, Sotax AG, Basel, Switzerland). Samples of 5 mL were automatically withdrawn at 5, 15, and 30 minutes, and 1, 2, 4, 6, and 8 hours without solvent addition. The starting volume of the dissolution vessels was 900 mL. All dissolution values were corrected for the volume reduction and drug loss within the sample volume. The 100% drug release values were calculated on the basis of the micro tablet theophylline content. Theophylline concentration was measured at a wavelength of 272 nm using an UV spectrophotometer (Lambda16, Perkin Elmer, Überlingen, Germany). The dissolution media were 0.01 M solutions of sodium nitrate, sodium sulfate, disodium succinate, succinic acid and sodium acetate or purified water. All dissolution media were prepared using purified water generated by reverse osmosis (Hemo-RO, Millipore, Bedford, MA) and following distillation (Muldestor, Wagner and Munz, München, Germany). The base chloride concentration of each dissolution medium was assayed using anionic chromatography (761 Compact IC, Metrohm, Herisau, Switzerland) (see below).

Chloride assay

The chloride concentration in the dissolution media, which resulted from the exchanged chloride ion of the micro tablet's Eudragit RS 30D coat, were measured via anionic chromatography (761 Compact IC, Metrohm, Herisau, Switzerland) employing a Metrosep Anion Dual 2 column (Metrohm, Herisau, Switzerland). The analytical column enclosed a cationic polymethacrylate polymer containing QAGs. To perform the assay, an alkaline buffer system containing 2.0 mM sodium hydrogen carbonate, 1.4 mM sodium carbonate, and 2.0% (wt/wt) acetone at a flux of 0.8 mL/min and a pressure of 4.9 to 5.4 MPa was used. The injection volume was 20 µL. The calibrated concentration range was 0.1 to 10 ppm Cl^- and the overall process standard deviation was calculated to 0.025 ppm. Migration times t_m are given in minutes.

Water content of isolated films

Isolated films were cut into stripes of 100 × 10 mm and immersed in the same dissolution media as described in section 1.4 for 3 hours at a temperature of 23°C. Vessels containing 50 mL dissolution media and the film sample, fixed in a plastic frame, were shaken (Type SS, Retsch KG, Haan, Germany). After swelling water droplets on the film surface were carefully removed, the water content was determined by Karl-Fischer titration using a 702 SM Titrino (Metrohm, Herisau, Switzerland) and the Metrodata software (Metrohm, Herisau, Switzerlan). All measurements were performed in 6 replicates. Films containing talc were dissolved in 30 mL pure methanol while films containing GMS as glidant were dissolved in 30 mL of a methanol-formamide mixture (1 + 1 (wt/wt)) because of limited solubility of these films in pure methanol. Further, 12 mL Hydranal solvent was added to the vessel and titration started using Hydranal Titrant 5 as titration solution, after the basic water content of the solution and the drift were determined.

Plasticizer leaching from isolated films

The films contained 20% (wt/wt) triethyl citrate as plasticizer and 8% (wt/wt) Tween 80 V as nonionic surfactant,

both calculated on the dry polymer weight. Both are water soluble and hence, leaching sensitive additives had an identical impact on the thermal properties of the polymer and could be summarized as plasticizer complex (PC).[10] Measuring the polymer's glass transition temperature T_G thus, led to the concentration of PC according to the calibration function stated below (Equation 3).[10]

$$\%PC = \frac{T_G^{-1} - b}{k} = \frac{T_G^{-1} - 3.003}{2.079.10^{-2}} \quad (3)$$

All T_G measurements were performed according to DIN 53765 using Mettler DSC 820 (Mettler-Toledo, Giessen, Germany). Samples of Eudragit RS films were swollen in 900 mL dissolution media at 37°C and stirred at 100 rpm. The swelling media were purified water and 0.01 M solutions of sodium nitrate, sodium sulfate, and sodium acetate. The film samples were removed from the swelling media after 5, 15, 30, and 60 minutes. After water droplets were removed, the films were dried in an oven for 24 hours at 45°C. Dry film samples with a mass of approximately 20 mg were sealed in aluminum pans, closed with perforated lids, and run at a heating and cooling rate of 20 K/min using nitrogen gas at a flux of 20 mL/min as blanket gas. The rest time in-between heating and cooling process was 2 minutes. For determination of T_G the second heating cycle was analyzed.

Statistics

All statistics, such as analysis of variance (ANOVA) and multiple range tests (Student-Newman-Keuls test), were performed using Statgraphics Plus 5.1 Professional Edition (Manugistics Inc, Rockville, MD) at probability levels of *P* as indicated in the text.

RESULTS

According to Wagner and McGinity,[9] monovalent anions comprising a small hydrodynamic radius (r_h) and, hence, a small hydrodynamic molar volume ($V_{h,m}$), should have an obstructive effect on the theophylline release through Eudragit RS 30 D membranes compared with anions with large hydrodynamic radius and volume, which displayed a release-enhancing effect. Contrary to the previously investigated acetate (r_h = 225.8 pm, $V_{h,m}$ = 29.03 cm^3/mol), the hydrodynamic radius (r_h) of nitrate was calculated to 129.0 pm and $V_{h,m}$ to 5.41 cm^3/mol (Table 2). These values are similar to the values of chloride (r_h = 123 pm, $V_{h,m}$ = 4.74 cm^3/mol), however the attraction of nitrate toward the QAG, ie, the selectivity coefficient, is higher compared with chloride,[11] resulting in a longer migration time of 9 minutes for the nitrate anion on the ion chromatography (IC) column against 4.5 minutes for chloride. For the divalent anions, sulfate ions were calculated to lower values of r_h (230.9 pm) and $V_{h,m}$ (31.04 cm^3/mol) compared with disuccinate anions (r_h = 307.1 pm, $V_{h,m}$ = 73.03 cm^3/mol) (Table 2), hence the crosslinking effect of divalent anions should be even more pronounced with sulfate ions, leading to more pronounced obstruction of drug release. Due to the generally higher selectivity coefficient of divalent anions toward QAGs, the migration times of sulfate as well as for disuccinate were prolonged compared with all monovalent anions investigated. However, the attraction of sulfate and disuccinate anions toward the QAGs of the IC column was almost

Table 2. Ion Properties in Aqueous Solution (Anion-limiting Conductivity as Presented in Falkenhagen et al[11])

Property	Unit	Cl^-	NO_3^-	SO_4^{2-}	$Succ.^{2-}$	$Hsucc^-$	OAc^-
Radius (anhydrous)*	(pm)	126	125	223	261	261	212
Molar volume (anhydrous)	(cm^3/mol)	5.06	4.93	29.1	44.85	44.85	23.97
Anion limiting conductivity (λ0−)	(cm^2/Ω*mol)	76.3	71.42	159.6	120	No data available	40.8
Hydrodynamic radius (r_h)	(pm)	123	129.0	230.9	307.1	No data calculable	225.8
Hydrodynamic molar volume ($V_{h,m}$)	(cm^3 / mol)	4.74	5.41	31.04	73.0	No data calculable	29.03
Hydrodynamic shell volume	(cm^3 / mol)	No hydration shell volume calculable	0.49	1.94	28.2	No data calculable	5.06
Migration time in anionic chromatography assay	(min)	4.30	9	14	14	1. Peak: 6†,‡ 2. Peak: 14†,§	3

*Anhydrous radii were taken from or calculated according to Wagner and McGinity.[9]

†Dissociation of succinic acid to monosuccinate‡ anion and disuccinate§ anion in the mobile phase of the anionic chromatography assay.

identical because the same retention time of 14 minutes resulted. For succinic acid, no data on r_h and $V_{h,m}$ could be calculated due to the lack of limiting anion conductivity data of mono succinate.[9] The retention time on the IC column of 6 minutes, however, indicated an attraction toward the QAG, ie, selectivity coefficient, in-between the chloride (4.5 minutes) and the nitrate (9 minutes) anion.

Generally, the published data for the selectivity coefficient values[11,12] and the measured migration times on the IC column were in the same order: sulfate > nitrate > chloride > acetate.

Dissolution of Theophylline

All dissolution profiles are depicted in Figure 1. In accordance with the values for r_h and $V_{h,m}$ the theophylline release of coated micro tablets depended on the anion species in the dissolution media and increased in the order nitrate < sulfate < disuccinate < succinic acid < acetate independent of the film composition (Figure 1). Neither the ionic strength of the media nor the pH value (Table 3) correlated with the different release rates in the order stated above. Despite succinic acid (pH 3.17), all other media ranged between 7.34 and 7.86. During 8 hours in nitrate media the membranes were almost sealed and showed a cumulative drug released after 8 hours between 0.04% and 0.25% of the entire dose. Only coat B containing 10% TEC and 5% GMS displayed a drug release of 4.27% after 8 hours. Coat B contained the lowest level of excipients, hence the volume fraction of the pure polymer was higher compared with the other coating compositions resulting in the highest QAG density of 270.8 μmol/cm^3. Drug release in sulfate media was similar compared with nitrate media resulting in a slightly higher total drug release between 0.38% and 3.14% (coats A, C, and D) and 9.38% for coat B. As in nitrate media an escalating drug release was observed exceeding a QAG density of 250 μmol/cm^3 within the polymer membrane. Disodium succinate ($Succ^{2-}$) as a divalent anion with similar attraction to the QAG than sulfate (migration time = 14 minutes) exhibited higher drug release rates as sulfate due to its larger hydrodynamic volume. The theophylline release after 8 hours ranged between 5.52% and 23.61% and increased with increasing QAG density. The monovalent monosuccinate ($HSucc^-$) increased the drug release further to 11.72% to 47.36% theophylline, however a plateau of drug release was apparently reached at a QAG density of 249.1 μmol/cm^3; the drug release values of 47.36 ± 0.55 and 45.56 ± 1.42 corresponding to a QAG density of 249.1 and 270.8 μmol/cm^3, respectively, were not statistically different (P = .99). Similar behavior was observed for the acetate anion. The anion with the least attraction toward the QAG (t_m = 3 minutes) showed, as expected, the highest cumulative drug release after 8 hours between 70.26% and 96.25%. Similar to the succinic acid medium, the most effective QAG density of the polymer was reached at 249.1 μmol/cm^3, since no significant difference (P = .95) between 94.06 ± 4.29 and 96.25% ± 2.37% theophylline release was found.

The drug release profiles showed a more or less linear course after a short lag time (Figure 1). The lag time in the dissolution media increased in the order acetate (5 to 15 minutes) < succinic acid (15 to 30 minutes) < disuccinate (30 minutes) and seemed to depend on the QAG density. As a trend a lower QAG density (coat D < coat A < coat C < coat B) resulted in a longer lag time (Figure 1), hence, talc-containing films resulted in longer lag times. For sulfate and nitrate media, which resulted in drug release rates of approximately zero, no lag time could be determined.

Chloride ion exchange

Consistent with earlier findings[9] the chloride ion exchanges showed completely different rates compared with the drug release profiles (Figure 2). After 60 minutes the chloride ion exchange reached an equilibrium at a level of 69% to 87% chloride in respect to the theoretical number of QAGs in the polymer and similar rates for sulfate, disuccinate, succinic acid, and acetate media. The divalent anions sulfate and disuccinate generally exhibited higher exchange levels than monovalent acetate and succinic acid media, except for coat B, where sulfate exchanged at a level of 69% of the QAGs even below the 75% level of acetate media. A completely different picture was displayed in nitrate media, which

Table 3. Concentration, Ionic Strength and pH of the Dissolution Media Investigated

Dissolution Medium	Sodium nitrate	Sodium sulfate	Disodium succinate	Succinic acid	Sodium acetate
Concentration (mol/L)	0.01	0.01	0.01	0.01	0.01
Ionic strength	0.01	0.03	0.03	0.003*	0.01
pH	7.34	7.50	7.86	3.17	7.62

*Dissociation of 0.01 M succinic acid in water ($H_2succ = 6.88 \times 10^{-3}$ mol/L, $Hsucc^{-1} = 3.12 \times 10^{-3}$ mol/L, $succ^{2-} = 2.04 \times 10^{-6}$ mol/L) taken from Wagner and McGinity.[9]

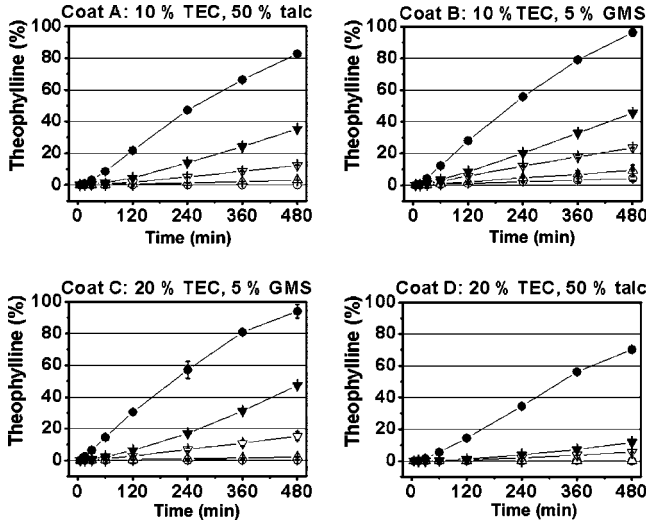

Figure 1. Theophylline release from Eudragit RS 30D–coated micro tablets (n = 3, mean ± 95% confidence interval. Symbols: ● = 0.01 M sodium acetate, ∇ = 0.01 M succinic acid, ▾ = 0.01 M disodium succinate, Δ = 0.01 M sodium sulfate, ○ = 0.01 M sodium nitrate).

exchanged chloride much slower and to a lower extent (31% to 58% QAG) without reaching an equilibrium (Figure 2). In contrast, acetate media, among those studied, always resulted in the fastest chloride ion exchange and the earliest time points for reaching the equilibrium.

The chloride ion exchange from talc-containing membranes (coat A and D) in 0.01 M sodium acetate media, displayed a chloride peak within the first 15 minutes, which is above the following chloride ion equilibrium in the medium. The 15-minute value of coat A (ρ_{QAG} = 194.6 mol/cm^3) showed a very high variability indicated by the large error bar (Figure 2), while the ion exchange for membranes of coat D (ρ_{QAG} = 183.2 mol/cm^3) showed even an exchange peak of high variation. This phenomenon, however, only occurred with talc-containing films (coat A and D) and was already noticed in a previous work.[9] An interaction between acetate and talc seems to be most likely, which was more pronounced the less extensive the ion exchange at the QAGs, ie, reduced QAG density. For the succinic acid, disodium succinate, sulfate, and nitrate media, the exchange rates of coat D were lower compared with the other coating membranes, especially for the exchange of sulfate ions, which reached their exchange equilibrium after 360 minutes compared with 60 minutes for the coats A to C.

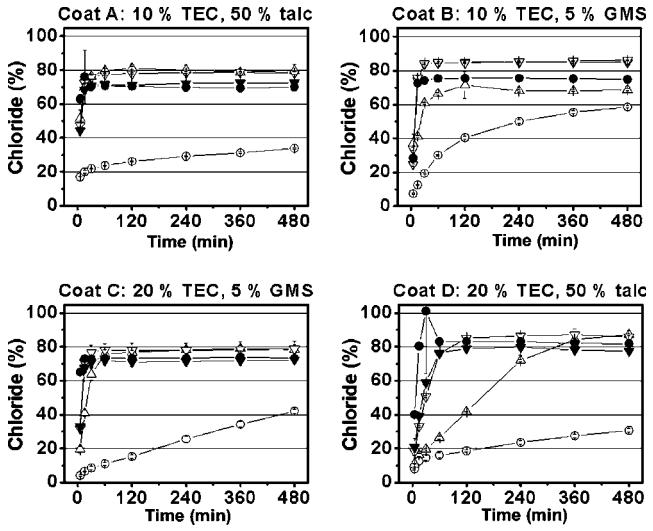

Figure 2. Chloride ion exchange from Eudragit RS 30D–coated micro tablets (n = 3, mean ± 95% confidence interval. Symbols: ● = 0.01 M sodium acetate, ∇ = 0.01 M succinic acid, ▾ = 0.01 M disodium succinate, Δ = 0.01 M sodium sulfate, ○ = 0.01 M sodium nitrate).

Water uptake of isolated films

As expected, the coating composition had a general influence on the water uptake. The more hydrophilic talc-containing films resulted in a 3.9% to 5.6% higher water content compared with the more hydrophobic GMS-containing films independent of all media tested except for nitrate media and purified water (Figure 3). For the 2 latter media no glidant effect could be seen; both film compositions resulted in the same water uptake (Figure 3). For glidant-containing membranes the divalent anions sulfate and disuccinate resulted in the lowest water content, 26.0% ± 0.5% (disuccinate medium) and 26.3% ± 0.3% (sulfate medium) for GMS-containing films and 30.8% ± 1.2% (disuccinate medium) – 30.2% ± 0.3% (sulfate medium) for films containing talc. Values following from monovalent acetate or succinic acid media were 6.6% to 8.9% higher, compared with the divalent anion media (GMS films: 32.6% ± 1.1% [acetate medium] and 33.4% ± 1.25% [succinic acid medium]; talc films: 38.3% ± 0.5% [acetate medium] and 38.9% ± 1.2% [succinic acid medium]). Although responsible for the lowest drug release for all coatings, the water

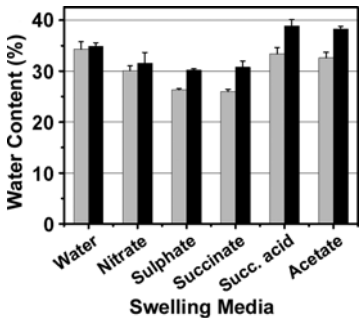

Figure 3. Water content of isolated Eudragit RS 30D membranes after swelling in various dissolution media (n = 6, mean ± 95% confidence interval, all dissolution media 0.01 M, ■ Eudragit RS 30D membrane containing 50% talc [Table 1, film I] ▨ Eudragit RS 30D membrane containing 5% GMS [Table 1, film II]).

content of the swollen membrane in nitrate media was in the range of 30.1% ± 0.9% (GMS film) and 30.9% ± 2.4% (talc film), which was about the same level as from GMS-containing films in acetate or succinic acid media, the media that enhanced strongly drug release. In order to check on the influence of the ion exchange on the water uptake, GMS and talc films were tested in demineralized water. Even in this medium the films incorporated 34.3% ± 1.5% (GMS film) to 34.9% ± 0.7% (talc film) water, however, similar to nitrate media, no difference between the GMS and talc films was observed (Figure 3). The Student-Knewman-Keuls test (P = .05) was performed to elucidate significant differences of the water content in GMS- and talc-containing films dependent on the anion species in the dissolution media (Table 4). There was no correlation found between the water content of the membranes after swelling and the theophylline release from micro tablets containing of the same coating.

Plasticizer leaching

Obviously, the polymer hydration did not have a decisive influence on the drug release through Eudragit RS 30 D membranes. But, if theophylline diffusion through the polymer membrane was not dependent on porosity caused by hydration and swelling,[1] a higher throughput of water or water flux could have caused the different dissolution profiles (Figure 1). In the latter case, other water-soluble film components like TEC and Tween 80 would be leached out from the polymer membrane dependent on the prevailing water flux to a different extent at different leaching rates. Both water-soluble components (TEC and Tween 80) could be summarized as plasticizer complex, thus their leaching off the film could be determined via the thermal properties of the polymer, ie, determination of the glass transition temperature, as shown in our previous work.[10] As succinic acid has been described as a potential plasticizer,[6] the plasticizer leaching was investigated for acetate, sulfate, and nitrate media. Acetate showed the highest leaching rate resulting in an equilibrium of 7.5% (wt/wt) plasticizer after 15 minutes. In contrast, leaching from films in nitrate media occurred much slower without reaching any equilibrium. After 60 minutes, 11% (wt/wt) plasticizer still remained in the polymer. Similar to acetate, the divalent sulfate media showed an equilibrium at 15% (wt/wt) plasticizer after 15 minutes, a higher level compared with that achieved by the acetate medium.

DISCUSSION

The effect of anions on drug release through Eudragit RS 30 D membranes was dependent on the attraction of the anions toward the polymer's QAGs. Mainly responsible for this attraction are the Coulomb forces,[5,9,11,12] which are inversely proportional to r_h^2, thus resulting in different selectivity coefficients of the exchange polymer toward the anion species. These findings were supported by the results of the IC. The anion exchange column used in IC consists of a polymethacrylate comprising QAGs, similar to Eudragit RS, hence the resulting migration time was also a measure of an anion's attraction toward the QAG of Eudragit RS. The migration times of the anions could therefore be used as a predictor for the selectivity coefficients in accordance with the published values[5,11] for strong basic anion exchangers. Thus, the smaller the r_h the higher the selectivity coefficient and the longer the migration time. However, due to the higher charge, divalent anions resulted in stronger attraction toward the QAGs, although their hydrodynamic radius is even higher than r_h of acetate. This can be explained by the interaction of each charge of a divalent anion with one single QAG[11,12] resulting in higher selectivity coefficients compared with monovalent anions. Due to the linear structure of the polymer chains the anions' cross-linking of the polymer chains resulting in reduced mobility and a more

Table 4. Results of Student-Newman-Keuls Test (P = .05) on Significant Differences of the Water Content After Swelling in Various Swelling Media*

		Water	Sodium nitrate	Sodium sulfate	Sodium disuccinate	Succinic acid	Sodium acetate
Film I (50% talc)	Water content ≈ 38%					■	■
	Water content ≈ 30%		▲	▲	▲		
Film II (5% GMS†)	Water content ≈ 33%	+				+	+
	Water content ≈ 26%			•	•		

*Identical Symbols Emblematizing films without significant differences in the water content after swelling.
†GMS, glycerol monosterate.

rigid polymer cluster was very likely. In this case, the shorter the distance between the 2 charges the shorter the cross-linking distance and the lower the mobility explaining the more obstructive effect on the theophylline release for sulfate compared with disuccinate media.

Still, it is not known how these different attractions toward the QAGs were mechanistically affecting the drug release properties of the Eudragit RS 30 D membrane.

The rates of the chloride ion exchanges indicated a fast exchange for all media except nitrate. The different degree of the anion's hydration could be responsible for a different degree of water uptake and subsequently, swelling. The hydrocolloid theory of higher drug permeability at higher swelling degree[1,2,4,13,14] is applicable to polymers like ethylcellulose and cellulose acetate. However, in the case of Eudragit RS 30D, disuccinate and sulfate media should have increased the drug release even more then acetate media, due to larger hydration shells at the same exchange level, which we did not observe (Figure 1). Also, the water uptake of isolated films in various media (Figure 3) did not correlate with the respective drug release profile (Figure 1). That means the different amounts of water in the polymer films were not responsible for the different drug release profiles.

Hence, drug diffusion was likely to be coupled with anion diffusion into and through the polymer membrane pulled by the electrostatic attraction of the QAGs. Despite the different attraction of the anions toward the QAGs, the equilibrium of the chloride ion exchange occurred to a similar extent and at similar rates except for the nitrate-containing media. However, as the extent and rate of the ion exchange was controlled by the excess of anions in the media according to the mass balance,[11,12] the mean residence time of an individual anion before being replaced by another one of the same species should be in the same order of magnitude as the attraction of the anion toward the QAG or the selectivity coefficient. In other words, anions displaying a strong attraction toward the QAG were supposed to have a long residence time at the QAG before being replaced, while anions of weak interaction forces should result in short residence times. Anion-specific residence times, however, would indicate a dynamic process of anions going back and forth to the QAG. In other words the oscillation of anions around the QAG was inducing a water flux. Thereby, the water flux was not dependent on the water uptake of the polymer, but on the QAG density within the polymer and the attraction of the anion toward the QAGs. The higher the QAG density the more likely the exchange of an anion from one QAG to another, enhancing the water flux. Any excipient used in this study, independent of its function as glidant or plasticizer, diluted the polymer and, hence, decreased the QAG density. So even higher plasticizer levels led to reduced drug release rates due to decreased QAG density despite the inverse effect of plasticizer for most of the nonionic coating polymers.[1,16] The effect of different anion attraction toward the QAG is depicted in Figure 4. Mainly 3 cases of interaction were responsible for the results in this study:

1. Chloride was exchanged against divalent anions like sulfate or disuccinate. Next to their strong attraction toward the QAGs (t_m = 14 minutes) they enabled cross linking. However, at a reduced QAG density (coat D) the likely distance between 2 QAGs, which was necessary for a divalent anion to bind, increased. As a consequence, the exchange rates in 0.01 M sulfate solution was sustained (Figure 2) due to the shorter distance of the 2 charges in the sulfate anion compared with the disuccinate. Both phenomena, high attraction forces, and cross linking would decrease the anion oscillation and, thus, hinder the water flux. Still, the disuccinate induced a water flux that resulted in a drug release after 8 hours between 6% and 24% due to size and hydration degree compared with sulfate. The smaller and less hydrated sulfate anion at similar attraction toward the QAG induced almost no water flux resulting in drug release of 0.4% to 10%. Because of the reduced water flux, the leaching rate of plasticizer was slower compared with acetate media and remained on an equilibrium level of 15.95% ± 0.96% after 15 minutes (Figure 4). The high equilibrium level might be related to the more rigid structure of the cross-linked polymer chains compared with the potentially higher mobility of polymer chains with QAGs substituted with monovalent anion species.
2. The small and almost nonhydrated nitrate anion (Table 2) showed the strongest attraction toward the QAG of all monovalent anions tested (t_m = 9

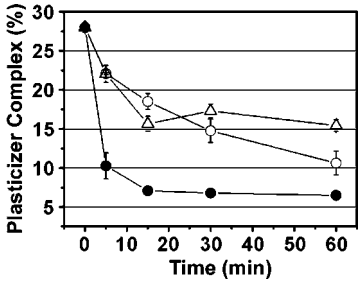

Figure 4. Scheme of interaction of Eudragit RS with various anion species (a = Cross linking: decelerated oscillation, hindered water flux, low permeability; b = Surface sealing: decelerated oscillation, hindered water flux, low permeability; c = "Active water carrier": permanent oscillation, induced water flux, high permeability).

minutes), which likely prevented any reexchange or oscillation. Since the exchange of chloride against nitrate ions occurred at the interface between dissolution medium and polymer membrane, the surface of the film exchanged nitrate first. Consequently, the water flux into deeper regions of the polymer film would be obstructed. This "sealing" effect was responsible for limited drug release through the membranes and a very slow rate of chloride ion exchange as well as for plasticizer leaching that occurred. However, equilibrium in the plasticizer content was not found to be dependent on the leaching time, for the reasons stated above in paragraph (1).

3. In contrast to case (2), the larger acetate anion showed the weakest attraction toward the QAGs (t_m = 3 minutes) and was very likely to enable high oscillations and water flux. Consequently, the highest theophylline release after 8 hours (Figure 1), the highest leaching rate of plasticizer at the lowest equilibrium level of 7.34% ± 0.35% after 15 minutes (Figure 5) could be observed. For monosuccinate the increased attraction toward QAGs (t_m = 6 minutes) would cause a smaller water flux and therefore reduced drug release compared with acetate, even when similar acetate and monosuccinate concentrations were used.[9] Still, drug release through Eudragit RS membranes was much higher for monosuccinate media (succinic acid) than for disuccinate or even sulfate or nitrate media.

CONCLUSIONS

From the reasons stated in the discussion section, the overall mechanism of drug release through Eudragit RS 30 D membranes can be depicted (Figure 6):

1. Water penetrates into the polymer membrane immediately. The absolute amount of water was dependent on the lipophilic character of the film, but this event did not significantly influence drug release.
2. The hydrated polymer was able to exchange the chloride ions of Eudragit RS against anion species being present in the dissolution medium. The ion exchange rate was completely different compared with the drug release. Eighty percent of the equilibrium level is exchanged within 60 minutes, except for nitrate media, which after exchanging

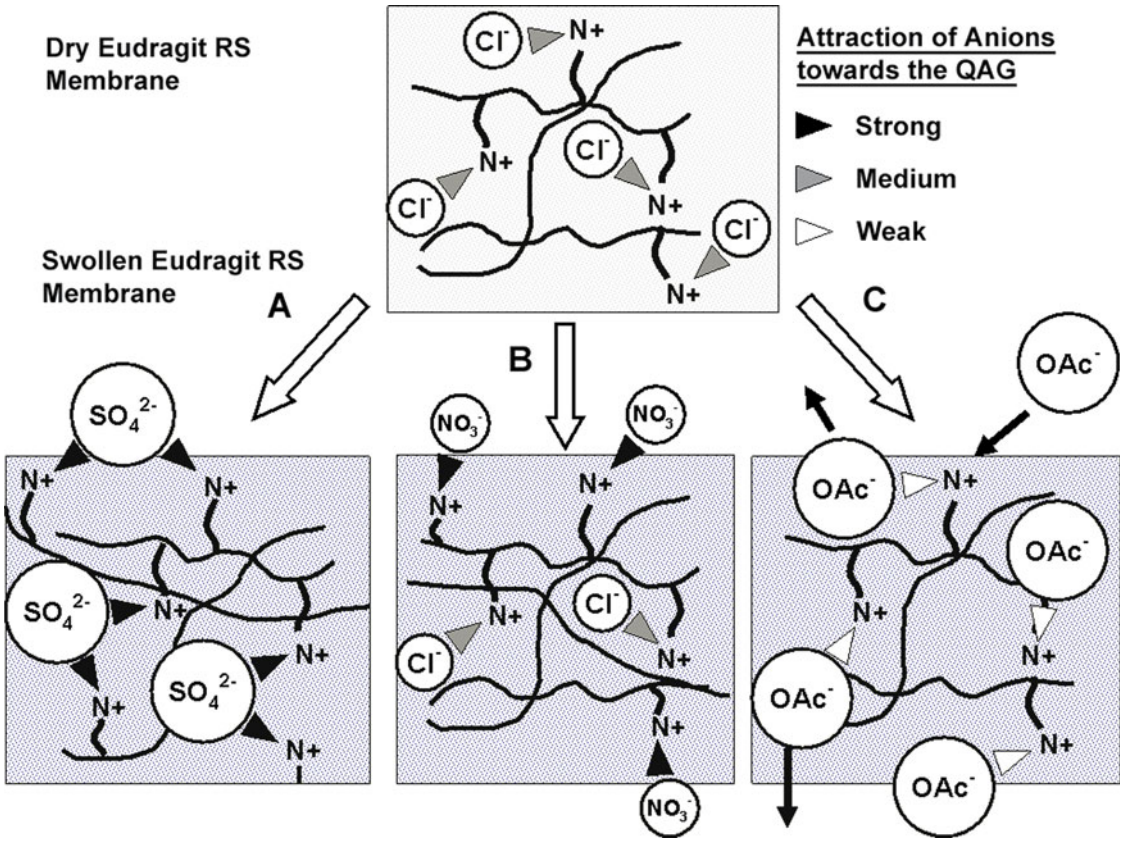

Figure 5. Plasticizer leaching from Eudragit RS 30D membranes (Table 1, film III) (n = 6, mean ± 95% confidence interval, media: ● = 0.01 M sodium acetate, Δ = 0.01 M sodium sulfate, ○ = 0.01 M sodium nitrate).

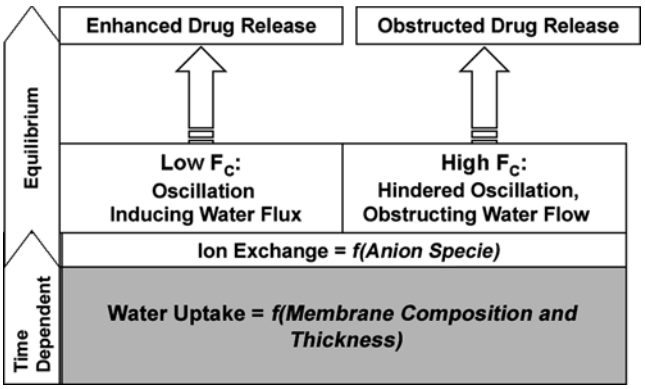

Figure 6. Drug release mechanism of Eudragit RS membranes (F_c = Coulomb force).

chloride on the polymer surface, obstructed further ion exchange in the inside.

3. Dependent on the attraction of the anion toward the QAGs, a water flux was very likely induced by back and forth exchanging or oscillating anions. High attraction forces or selectivity coefficients (nitrate, sulfate) hence resulted in a low water flux, while low attraction forces or selectivity coefficients, respectively, resulted in a high flux (acetate, succinic acid).
4. The water flux and, hence, the drug release increased with higher QAG density of the polymer membrane. Any excipient, whether glidant or plasticizer, was acting as a diluent for the QAG density. Therefore, in contrast to other polymers, higher plasticizer concentrations led to lower drug release.

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